CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20689

CORRESPONDENCE

ORIGINAL

Alan L. Bess, M.D.
Vice President
Pharma Development Safety

SUPPL NEW CORRESP
(SNC)

NDA 20-689

Roche

Pharmaceuticals

July 1, 1998

Raymond J. Lipicky, M.D.
Center for Drug Evaluation and Research
Division of Cardiorenal Drug Products
HFD 110
1451 Rockville Pike
Rockville, Maryland 20852

Dear Doctor Lipicky,

In follow-up to our letter of June 22, 1998 and pursuant to 21CFRS314.90, we are hereby requesting a waiver of reporting requirements for safety reports involving Posicor. All Posicor ADR reports are being prioritized, so that serious events are handled promptly. Our goal remains, to submit to the agency within 15 calendar days all serious, unlabeled adverse event reports - the present situation may preclude us meeting this requirement in all cases. We will make every effort to have all serious unlabeled reports to the agency within 30 working days from their due date.

Due to the increased volume, we have enlisted the help of other groups within Roche to assist with incoming calls. This has contributed to a delay in some reports reaching Drug Safety. Additionally, we anticipate delays in processing of cases at our Global Drug Safety Processing Center in the UK, in our quarterly Posicor reports and in obtaining follow-up information on cases within the timeframe outlined in our local SOP's. Therefore, we are requesting a delay in the anticipated receipt date of our Periodic Report for Posicor, due July 19, to September 19, 1998.

Please contact me if you wish to discuss this further.

Sincerely,

Alan L. Bess, M.D.

ALB/tjp

cc: D. Roeder

Hoffmann-La Roche Inc. 340 Kingsland Street Nutley, New Jersey 07110-1199 Tel. 973-562-3512 Fax 973-562-3563

ROCHE DRA

Voluntary Market Withdrawal
All Lots: Posicor 50 mg and 100 mg Tablets
NDC #s: 0004-0080-01, 0004-0080-27, 0004-0080-49,
0004-0081-01, 0004-0081-49

June 8, 1998

Dear Doctor:

Roche Laboratories announced today the voluntary market withdrawal of the antihypertensive and anti-anginal medication Posicor® (mibefradil dihydrochloride).

The company is taking this action based on evolving information concerning the potential for drug interactions, some of them serious, that may occur when Posicor is taken together with some other medications. The decision follows the analysis of the preliminary results of a three-year long-term study of Posicor in congestive heart failure. The study demonstrated no overall difference between Posicor or placebo when added to standard therapy in this patient population, but it provided further information on drug interactions.

In both hypertension and chronic angina pectoris, Posicor has consistently proved to be effective and well tolerated, when used appropriately; however, the combination of Posicor and some other commonly used drugs, among them cardiovascular agents, may increase the frequency of the side-effects of these other medications. In principle, drug interactions can be addressed by appropriate labeling; however, with respect to Posicor, Roche Laboratories believes that the complexity of such prescribing information would make it too difficult to implement. As patient well-being is of highest priority to Roche, the company has decided to voluntarily withdraw the compound from the market.

The company is working closely with the Food and Drug Administration to inform physicians and other health care professionals of its decision.

Please immediately discontinue prescribing and dispensing Posicor, and immediately contact your patients who are currently prescribed Posicor so that they can discontinue treatment and receive appropriate alternative therapy. To receive a refund, patients should be instructed to immediately return any unused Posicor tablets via regular US mail to the following address:

Capital Returns, Inc.
ATTN: CVRET
4066 N. Port Washington Road
Milwaukee, WI 53212

Patients must include the following information when returning any unused Posicor tablets:

Name
Address
Unused product in original pharmacy packaging
Pharmacy receipt

Patients will receive a refund based on the value of the number of tablets returned, not to exceed the price paid on the receipt, plus the cost of shipping via regular U.S. mail.

Effective immediately, the Posicor compliance program, PosiCare, will be discontinued.

In order to ensure a smooth return process, it is very important that you fill out and return the enclosed Business Reply Card (BRC). In addition, if you have any Posicor samples (50mg or 100mg tablets) in your office, please use the enclosed UPS shipping label(s) to return the samples to Capital Returns, Inc. at the same address listed above and on the shipping label. Please include your return address on each label.

If you have any questions, please call Roche Laboratories at 1-800-205-4611.

Sincerely,

Russell H. Ellison, MD
Vice President
Medical Affairs

Roche

Pharmaceuticals

Dear Doctor: December 1997

We would like to inform you of important new warning information concerning the use of POSICOR® (mibefradil dihydrochloride), a treatment for hypertension and chronic stable angina pectoris. This concerns:

1. a warning related to suppression of sinoatrial activity and severe bradycardia occurring with POSICOR, and
2. a warning and contraindication concerning drug interactions and statin-induced rhabdomyolysis with POSICOR and certain HMG-CoA reductase inhibitors.

This letter emphasizes the importance of patient selection, patient monitoring, and attention to concomitant drug therapy to ensure that POSICOR is used appropriately. Please see enclosed complete product information.

I. Decreased Sinus Node Activity and Severe Bradycardia

The use of POSICOR has been associated with the appearance of symptomatic slow junctional rhythm. Ventricular rates have been as low as 30 to 40 bpm and many patients have been symptomatic. To date there have been about three dozen such reports arising from an exposure of 75,000 patients. This adverse effect has occurred mainly in elderly patients who were on concomitant beta-blocker therapy. Similar findings of symptomatic slow junctional rhythm have also been reported with other heart rate lowering compounds such as beta-blockers, digoxin, diltiazem and verapamil, especially when more than one of these agents are used at the same time.

In order to assist you in the appropriate use of POSICOR, please review the following package insert revision:

> **WARNINGS:** ***Suppression of Sinoatrial Node Activity:*** **Use of mibefradil has been associated with slowing or complete suppression of sinoatrial node activity. The supervening junctional rhythms have often been slow (as slow as 30 to 40 bpm). Many of the reports have incorrectly identified the adverse event as complete AV block. The reports have been most common in the elderly, mainly in association with the concomitant use of beta-blockers. Care should be taken when combining POSICOR with beta-blockers, particularly when pretreatment sinus rate is below 55 bpm, and this combination should be avoided in the elderly when pretreatment sinus rate is below 55 bpm (see PRECAUTIONS). In patients with low heart rates, use of any combination of agents that can slow the sinus node or affect the AV node (eg, beta-blockers, digitalis, and the calcium channel blockers mibefradil, diltiazem, and verapamil) should in general be undertaken only after careful consideration, as such combinations can unmask underlying sick sinus syndrome. Use of POSICOR in patients with sick sinus syndrome without a pacemaker is contraindicated (see CONTRAINDICATIONS).**

POSICOR is associated with a dose related decrease in heart rate. This effect is achieved whether POSICOR is given as monotherapy or in combination with beta-blockers. In susceptible patients, as described in the revised warnings section, the decrease in sinus node activity may result in severe sinus bradycardia or sinus arrest. In reported cases, cardiac pacing has been taken over by the AV node, but sometimes at low rates that were poorly tolerated.

Roche Laboratories Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

II. Interaction of POSICOR (mibefradil dihydrochloride) with certain HMG-CoA Reductase Inhibitors

Roche has received 7 domestic reports of statin-induced rhabdomyolysis in patients receiving simvastatin and POSICOR (4 of the cases were also receiving cyclosporine), presumably due to inhibition by POSICOR of the metabolism of simvastatin, markedly increasing simvastatin's plasma concentration. POSICOR is a strong inhibitor of cytochrome P450 3A4, the enzyme responsible for metabolizing several of the HMG-CoA reductase inhibitors. POSICOR also inhibits metabolism of cyclosporine, increasing its blood levels; cyclosporine itself decreases excretion of all HMG-CoA reductase inhibitors and substantially increases their blood levels.

POSICOR would be expected to have effects on blood levels of certain other HMG-CoA reductase inhibitors. Based on the similarity of lovastatin and simvastatin metabolism, coadministration of POSICOR and lovastatin would also be expected to result in markedly increased plasma concentrations of lovastatin. Atorvastatin and cerivastatin are also metabolized by CYP450 3A4, but the metabolites are active, so the overall effect of POSICOR on their HMG-CoA reductase activity may not be large. Studies of atorvastatin and cerivastatin with erythromycin, a moderate inhibitor of CYP450 3A4, have not shown marked increases in the blood levels of these HMG-CoA reductase inhibitors, but at present there are no studies with stronger inhibitors, such as mibefradil, ketoconazole, or itraconazole.

Since fluvastatin and pravastatin are not significantly metabolized by CYP450 3A4, POSICOR would not be expected to have a significant effect on their blood levels. Please see enclosed complete product information.

In order to assist you in the appropriate use of POSICOR, please review the following package insert revisions:

- **CONTRAINDICATIONS:** POSICOR is contraindicated in patients who:

  Are concurrently receiving terfenadine, astemizole, cisapride, lovastatin or simvastatin (see WARNINGS and PRECAUTIONS).

  WARNINGS: ***Interaction Resulting in HMG-CoA Reductase Inhibitor-Induced Rhabdomyolysis:*** **Mibefradil inhibits the action of CYP450 3A4. When this enzyme is inhibited, plasma concentrations of those drugs that are metabolized by CYP450 3A4 may become elevated, sometimes by more than an order of magnitude (see PRECAUTIONS).**

- **Rhabdomyolysis is a known rare adverse effect of all of the HMG-CoA reductase inhibitors (the "statin" cholesterol-lowering agents).**

  The statins are not identically metabolized:

  - **Lovastatin and simvastatin are dependent on CYP450 3A4 for their metabolic clearance. Among patients receiving simvastatin and mibefradil there have been reported cases of rhabdomyolysis. These events appear to reflect an incidence of rhabdomyolysis higher than that seen during treatment with simvastatin alone. Because of the metabolic similarities of lovastatin and simvastatin, coadministration of POSICOR with either of these two drugs is contraindicated.**

  - Atorvastatin and cerivastatin are biotransformed by CYP450 3A4 to active and inactive metabolites. Also, only small changes in HMG-CoA reductase inhibitor activity have been seen in studies where atorvastatin and cerivastatin were combined with erythromycin (a less potent CYP450 3A4 inhibitor than mibefradil). Nevertheless, until there is more information on the coadministration of CYP450 3A4 inhibitors (including mibefradil) with atorvastatin and cerivastatin, coadministration of either of these two drugs with POSICOR should generally be avoided.

- Fluvastatin and pravastatin are not significantly metabolized by CYP450 3A4; no clinically important interaction with mibefradil is anticipated. Therefore, no specific dose adjustment of fluvastatin or pravastatin is recommended with coadministration of POSICOR (mibefradil dihydrochloride).

Drug Interactions - Cyclosporine/Tacrolimus and HMG-CoA Reductase Inhibitors:
The calcineurin immunosuppressants tacrolimus (FK-506) and cyclosporine are metabolized by CYP450 3A4, so their blood levels rise (in the case of cyclosporine, about twofold) when POSICOR is coadministered; dose adjustment may be necessary. Because the immunosuppressants themselves inhibit a drug-transport system that participates in the excretion of HMG-CoA reductase inhibitors, elevated levels of the immunosuppressants can cause additional elevations in the blood levels of any of the HMG-CoA reductase inhibitors. **Use of POSICOR should be avoided in patients also receiving both a calcineurin immunosuppressant and an HMG-CoA reductase inhibitor.**

We trust this information will assist you in using POSICOR to manage your hypertensive and angina patients appropriately. Please see enclosed complete product information.

If you have any questions about POSICOR, we encourage you to call the toll-free number for Roche Medical Services at 1-800-526-6367. Also, if you are aware of any serious adverse events potentially associated with the use of POSICOR, please report such information to Roche at the above number or the Food and Drug Administration MedWatch program at 1-800-FDA-1088.

Sincerely,

Russell H. Ellison, MD
Vice President
Medical Affairs

ORIGINAL

Roche

June 16, 1998

Division of Cardio-Renal Drugs Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
ATTN.: DOCUMENT CONTROL ROOM NO. 5002
1451 Rockville Pike
Rockville, Maryland 20852

Ladies and Gentlemen:

Re: NDA 20-689 -- Posicor® (mibefradil dihydrochloride) Tablets
Response to Request for Information: Rationale for Therapy Substitution

In response to Dr. Robert Temple's request, we are herewith submitting the rationale for recommended therapy substitution upon withdrawal of Posicor.

If you should have any questions regarding this submission, please contact the undersigned.

Sincerely,

HOFFMANN LA-ROCHE INC.

Rudolph W. Lucek

Rudolph W. Lucek
Group Director
Drug Regulatory Affairs

(973) 562-3688 (Phone)
(973) 562-3554/3700 (Fax)

Attachment
HLR No. 1998-1560

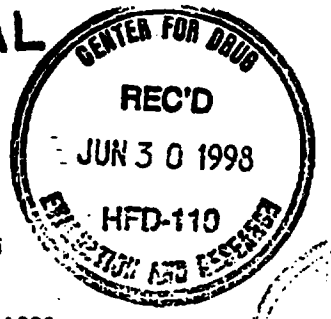
Desk Copy: Mr. David Roeder

ORIGINAL

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

ORIGINAL

Alan L. Bess, M.D.
Vice President
Pharma Development Safety



Roche

N 20-689

June 22, 1998

Central Document Room
Food and Drug Administration
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20852

SNC 6 M-5006

Dear Sir / Madam:

Pursuant to 21CFRS314.90, we are hereby requesting a waiver of reporting requirements for safety reports involving Posicor. Since release of the June 8 and June 15, 1998 letters to health care professionals regarding the market withdrawal of Posicor (see attached), Roche has been receiving approximately 3000 telephone calls daily involving Posicor. Of these, approximately 100 initial and follow-up telephone reports regarding possible Posicor adverse events have been received daily, which is 6-8 times the normal volume. The majority of these calls are from consumers, and are non-serious. The reports are being prioritized, so that serious events are handled promptly. Our goal remains, to submit to the agency within 15 calendar days all serious, unlabeled adverse event reports - the present situation may preclude us meeting this requirement in all cases.

Due to the increased volume, we have enlisted the help of other groups within Roche to assist with incoming calls. This has contributed to a delay in some reports reaching Drug Safety. Additionally, we anticipate delays in processing of cases at our Global Drug Safety Processing Center in the UK, in our quarterly Posicor reports and in obtaining follow-up information on cases within the timeframe outlined in our local SOP's.

Additionally, we are requesting a delay in the anticipated receipt date of our Periodic Report for Posicor, due July 19, to September 19, 1998.

Please contact me if you wish to discuss this further.

Sincerely,

Alan L. Bess, M.D.

ALB/tjp
Enclosure

cc: N. Haggard
D. Barash
R. Lillie
R. Lipicky

ORIGINAL

Hoffmann-La Roche Inc. 340 Kingsland Street Nutley, New Jersey 07110-1199 Tel. 973-562-3512 Fax 973-562-3563

JUL 22 1998

NDA 20-689

Hoffmann-La Roche Inc.
Attention: Mr. Rudolph Lucek
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Mr. Lucek:

Please refer to your new drug application for Posicor (mibefradil dihydrochloride) Tablets.

We also refer to the submissions dated June 22 and July 1, 1998, in which a waiver of reporting requirements for safety reports involving Posicor was requested.

As discussed in your July 13, 1998 telephone conversation with Mr. David Roeder of this Division, your request is granted. We understand that you will make every effort to submit to the agency within 15 calendar days all serious unlabeled adverse event reports. In light of the unusually high volume of reports associated with the withdrawal of Posicor from the market, however, we understand that you may not be able to meet that goal in all cases. In cases where it is not possible to submit the reports within 15 calendar days, it is acceptable to report them within 30 calendar days of the due date. Please note that this waiver pertains only to adverse event reports related to Posicor. We also grant your request to delay the submission of your next periodic report from July 19 to September 19, 1998.

If you have any questions, please contact:

Mr. David Roeder
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival NDA 20-689
HFD-110/Div. Files
HFD-110/D.Roeder
HFD-735/SLu
HFD-735/DBarash
HFD-730/RLillie
DISTRICT OFFICE
Drafted by: dr/July 14, 1998;sb/7/16/98
Initialed by: G Buehler for N Morgenstern
filename: N20689_G

GENERAL CORRESPONDENCE